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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,997	12/24/2003	Yukio Nihei	245553US0CONT	9427

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/743,997	NIHEI ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-42 and 50-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-42 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed **3/11/08** presents remarks and arguments to the office action mailed **9/11/07**. Applicants' request for reconsideration of the rejection of claims in the last office action has been considered.

Applicants' arguments, filed, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 39-42 and 50-56 are pending.

Claims 1-38 and 43-49 are cancelled.

Claim Objections

Claim 39 is objected to because of the following informalities: part b of the instant claim is limited to only one compound and the a in front of tubulin should be changed to the. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-42 and 50-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Malignant fibrous histiocytoma, MC-9, does not reasonably provide enablement for a very wide variation of cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Nature of the Invention: The claims are drawn to method for treating tumors which comprises administering to a subject in need thereof a composition comprising an effective amount of an anti-inflammatory active substance dexamethasone and AC-7700 and a salt thereof. The nature of the invention is extremely complex in that it encompasses the treatment of a wide variation of tumors.

Breath of the Claims: The complex of nature of the claims is very broad.

Predictability of the Art: The lack of significant guidance from the specification as to how a very wide variety of cancers or tumors can be treated with this composition makes practicing the claimed invention unpredictable in terms of treatment to a wide variation of tumors. As taught by Li et al. (Expert Opinion Ther. Patents (2002), 12(11) 1663-1702) AC-7700 is an antimitiotic agent with tubulin binding site. These antimitotic agents are not truly selective antitumor agents. Also, that combrestatin shows poor efficacy in vivo. See pages 1664and 1667 underlining. Also, AC-7700 even though it exhibits good in vivo efficacy against several advance solid tumors it is noted that tubulin binding agents appear to fail in human trials despite demonstrating good preclinical efficacy. One reason appears to be a large difference between the tolerated dosages in human clinical trials and those determined in the preclinical animal models.. See underling pages 1668 and 1691.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39-42 and 50-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nihei et al. Jpn. J. Cancer Res. 90, 1016-1025, Sept.,1999, taken with Hori et al. ,Med. Sci Monit, in view of Fex et al., US 3,732,260 and Sugawara et al., US 6,458,347 (all references are of record)

The Nihei et al. teach the combination of dexamethasone (an anti inflammatory agent) with AC 7700 ((Z)-N-[2-methoxy-5[2(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide), a tubulin polymerization-inhibitory active substance (see page 1023, lft col. last five lines) as required by instant claims 1, 30, 32 and 35. Please note that MPEP 2112.01 states "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Nihei et al. teach treating human carcinogens. Nihei do not however, teach the use of the compounds as one anti-tumor agent, but rather separately. As to the demethasone being a salt or an ester is within the purview of the skilled artisan to make and optimize as required by instant claims 52-54.

Hori et al. teach AC 7700,((Z)-N-[2-methoxy-5[2(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide), (see abstract) as an anti –cancer agent, with anti-cancer activity as required by instant claim 39 in part, wherein the unit dosage of the AC 7700 is 10 mg/kg in a unit dosage (see page 28 highlighted), as required by instant claim 41, wherein 10 mg/kg is within the claim limitation, for example, if the weight of the patient is 50 kg, then the unit dose is 500 mg. Please note that AC 7700 is combrestatin-4, thus making claims 39, 55-56 obvious variations and within the purview of the skilled artisan to make various salts and test there potency, this is a common practice for a chemist.

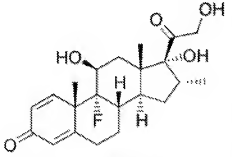
Fex et al. teach administration of steroidal compounds with other pharmaceutically active agents (see col. 4 lines 33+), wherein the unit dose of the steroid is 10-100 mg (see col. lines 33-61) as required by instant claims 42 and 51. Also Fex teaches the compounds (steroids) can be used in treatment with any anti-cancer agent (see col. 2 lines 15+) simultaneously or sequentially as in claims 50-51. Adjuvant therapies may be administered either together as a combination, separately, or sequentially. This is a well known fact in the art of adjuvant therapy, and one of ordinary skill in the art would have known how to administer the drugs.

Sugawara et al teach a complex drug formulation comprising and anticancer cancer drug taxane (an anti cancer agent class of vinca alkaloids that destroy mitotic bundles) and betamethasone (see col. 4, lines 50-67). In view of this disclosure, one of ordinary skill in the art would have been motivated to combine the teachings to Fex et al. with that of Sugawara et al, substitute the taxane drug disclosed by Sugawara et al

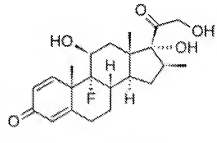
to AC-7700 and combine with a steroid to form a single agent for the treatment of cancer.

One of ordinary skill in the art would have being motivated to combine the teachings of Nihei with that of Hori et al. to arrive at the instant subject matter. Since Nihei et al. teach the combination of both drugs, one of ordinary skill in the art would have been motivated to make and use the claimed invention at the time the invention was made. Nothing unobvious is seen in doing so.

Examiner has drawn the structure of dexamethasone and betamethasone for Applicants comparison as to why one of skill in the art would easily substitute one for the other as A prima facie case of obviousness may be based solely upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. In re Deuel, 51 F3d. 1552, 1559 (Fed. Cir. 1995). The necessary motivation to make the claimed compound, and thus the prima facie case of obviousness, arises from the reasonable expectation that compounds similar in structure will have similar properties. In re Gyurik, 596 F.2d 1012, 1018 (1979).



Dexamethasone



Betamethasone

It is *prima facie* obviousness to select a known material based on its suitability for its intended use. *See Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65

USPQ 297 (1945). Also, established precedent holds that it is generally obvious to add known ingredients to known compositions with the expectation of obtaining their known function. See, e.g., *In re Linder*, 457 F.2d 506, 507 (CCPA 1972); see also *In re Dial*, 326 F.2d 430, 432 (CCPA 1964).

The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Also as stated in the MPEP, the rationale for combining references is a recognition, expressly or impliedly in the prior art, or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Since these agents are known for there specific functions, integrating them would not differ, as each will be considered to function independently. The properties will still be the same whether separately or combined in one.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

Response to Argument

Applicant argues that the showing of unexpected result in Figures 1 and 2 should overcome the above rejection.

In response, the unexpected result are not commensurate with the claims. The claims are to a very wide variation of tumors and only to dexamethasone while the unexpected result is to only Malignant fibrous histiocytoma, MC-9 (see page 22 of the specification and the compounds include esters thereof.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

SVG
5/29/08